**Remarks**

The Office Action dated June 18, 2002 has been carefully reviewed and the foregoing amendments are made in response thereto. In view of these amendments and the following remarks, Applicants respectfully request reconsideration and reexamination of this application and the timely allowance of the pending claims.

Claims 3-22 have been cancelled without prejudice or disclaimer of Applicants' right to pursue the subject matter of these claims in a divisional application and claims 23-36 have been added. The specification has been amended to add sequence identifiers to the text. Applicants respectfully submit that no new prohibited matter has been introduced by these amendments. Written description support for the additional claims can be found throughout the specification and in the original claims. Specific support for claims 23-36 can be found on the pages as set forth in the table below.

| Claims | Written Support |
|---|---|
| 23 | page 3, lines 8-10 |
| 24-25 | page 2, lines 29-31; page 3, lines 1-4 |
| 26-27 | page 8, lines 12-14 |
| 28, 30 | page 7, lines 20-24 |
| 29 | original claim 21 |
| 31-33 | page 7, line 18-20 |
| 34-35 | page 3, lines 11-14 |
| 36 | page 3, lines 14-16 |

**Summary of the Office Action**

1. Applicants' election with traverse of Group I in Paper No. 10 was recognized. The claims of Group VI were rejoined to the claims of Group I.

2. The specification was objected to for not containing a brief description for Figures 1 and 2.

3. The specification and claims were objected to for failing to adhere to the requirements for applications containing nucleic acid and amino acid sequences.

4. Claims 3-6, 16 and 21 were rejected under 35 U.S.C. 112 (second paragraph) as being indefinite for failing to particularly point out and distinctly claim the subject matter regarded as the invention.

5. Claims 3-6, 16 and 21 were rejected under 35 U.S.C. 112 (first paragraph) for containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the Applicants had possession of the claimed invention.

6. Claims 2-4 were rejected under 35 U.S.C. 102(b) as being anticipated by Sala *et al.* (1994) J. Virol. 68, 5280-5283.

7. Claim 6 was rejected under 35 U.S.C. 103(a) as being unpatentable over Sala *et al.* (1994) J. Virol. 68, 5280-5283.

8. Claims 6 and 16 were rejected under 35 U.S.C. 103(a) as being unpatentable over Sala *et al.* (1994) J. Virol. 68, 5280-5283 in view of Haynes *et al.* (U.S. Patent 5,019,387).

**Response to the Office Action**

The disclosure was objected to for failing to have a brief description of Figures 1 and 2. Applicants bring to the Examiner's attention that beginning on page 3, line 23 to page 4, line 12 of the specification where a brief description of Figures 1 and 2 is disclosed. In light of this disclosure, Applicants respectfully request that the objection be withdrawn.

The specification and claims were objected to for failing to adhere to the requirements for applications containing nucleic acid and amino acid sequences. Applicants respectfully submit the enclosed corrected sequence listing and computer readable form of the sequence listing. In addition, amendments have been made to the specification to add sequence identifiers to the text. In light of these amendments, Applicants respectfully request that the rejection be withdrawn.

**Rejections under 35 U.S.C. 112 (second paragraph)**

The Office Action rejected claims 3-6, 16 and 21 under 35 U.S.C. 112 (second paragraph) purportedly because the claims as written failed to particularly point out and distinctly claim the subject matter of the invention. These claims have been cancelled, therefore the rejection is moot. In light of the substitute claims, however, Applicants respectfully submit that these substitute claims particularly point out and distinctly claim the subject matter of the claimed invention.

Specifically, the Examiner objected to the term "fragment" as being unclear in its limitations. The fragments recited in claims 24 and 25, in addition to containing the recited amino acid residues at positions corresponding to residues 313, 314 and 325 of SEQ ID NO: 1, are limited to those peptide fragments that induce the production of anti-serum that is broadly cross-reactive *in vivo* against multiple strains of HIV-1. In a similar manner, claims 5, 6 and 16 have been rewritten as claims 33-36, so that the "fragment" provides the structural feature of the recited amino acids at these positions and the functional feature of induction of a cross-reactive neutralizing anti-serum.

**Rejections under 35 U.S.C. 112 (first paragraph)**

Claims 3-6, 16 and 21 were rejected under 35 U.S.C. 112 (first paragraph) for purportedly containing subject matter which was not described in the specification in such a way as to reasonably convey to the skilled artisan at the time of the invention, that Applicants were in possession of the invention. Although Applicants disagree with this position, these claims have been cancelled in favor of new claims 23-36. In light of these substitute claims, Applicants respectfully submit the substitute claims define the claimed invention in such a manner as to reasonably convey to the skilled artisan that Applicants were in possession of the claimed invention.

The Office Action states that the animal model employed in Example 9 of the present application does not provide evidence that the instant composition provides protection in humans (see Office Action at page 6, lines 20-21). The Examiner appears to be confusing the experimental data in Example 9 as a murine *in vivo* model for HIV infection. A careful reading of Example 9 indicates that Applicants were able to raise antibodies against HIV in mice by injection of recombinant expression vectors encoding the claimed HIV envelope proteins. Following isolation of these antibodies from mice, Applicants demonstrated that these antibodies were effective in neutralizing a wide variety of HIV-1 primary isolates and laboratory-adapted strains using the *in vitro* neutralization assay as disclosed on page 24 of the specification. Thus, Applicants were able to use the envelope proteins to generate antibodies in an animal model for generating antibodies, and the antibodies were effective in neutralizing multiple strains of HIV *in vitro*. Applicants therefore submit that the specification provides adequate support claims directed to the claimed methods and compositions.

Applicants bring to the attention of the Examiner that the *in vitro* neutralization assay employed in the working examples of the specification is widely accepted in the field of HIV research as a measure for determining the ability of an antibody to neutralize entry of HIV into a cell. As support for this statement, Applicants have attached a publication (Zhang *et al.* (2002) J. Virol. 76, 644-655) from a peer-reviewed journal (published after the priority date) which discloses immunization of mice with a claimed composition and isolation of antibodies from the immunized mice that were capable of generating a broadly cross-reactive neutralizing response to multiple strains of HIV-1 *in vitro*. Applicants submit that the specification provides all the experimental data necessary for the claimed vaccine composition.

Furthermore, the Examiner indicates that there are no acceptable animal models for HIV infection (see Office Action at page 6, lines 21-22). In this regard, Applicants bring to the attention of the Examiner that they are not required to provide clinical data to demonstrate enablement of the claimed

invention (see *In re Brana* 51 F.3d 1560 and *In re Isaacs* 347 F.2d 889). Thus, in the absence of clinical data in humans, Applicants submit that they have provided all the experimental data necessary to demonstrate that the claimed immunogenic and vaccine compositions are capable of generating an antibody that is which neutralizes multiple strains of HIV-1 *in vitro*.

**Rejections under 35 U.S.C. 102(b)**

Claims 2-4 were rejected under 35 U.S.C. 102(b) as being anticipated by Sala *et al.* or Lukashov *et al.* With regard to claim 2, the Office Action states that although Sala *et al.* does not disclose the entire amino acid sequence of SEQ ID NO: 1 and that this sequence would be an inherent property of the envelope protein disclosed in this reference (see Office Action at page 8, lines 1-2). Applicants respectfully disagree. Sala *et al.* do not disclose the complete HIV-1 protein sequence comprising SEQ ID NO: 1 and therefore do not disclose each and every element of claim 1. Furthermore, the Office Action indicates that "hypervariability of sequences among the different HIV strains is a well recognized concern in the HIV art" (see Office Action at page 6, lines 14-15). Given this statement, it does not seem possible that one can assume that a partial sequence of an envelope protein would have one-hundred percent sequence identity in the remainder of the envelope protein sequence. In the absence a disclosure of a sequence comprising SEQ ID NO: 1, Applicants request that the rejection of claim 2 be withdrawn.

With regard to claims 3 and 4, these claims have been cancelled and the rejection is therefore moot. Applicants bring to the attention of the Examiner that claims 3 and 4 have been rewritten as claims 24 and 25. These substitute claims provide the functional feature that the claimed envelope protein be capable of generating a cross-reactive neutralizing antiserum against multiple strains of HIV-1 *in vitro*. Neither Sala *et al.* or Lukashov *et al.* disclose this feature of the claimed envelope protein let alone the claimed structure. Furthermore, neither of the cited references discloses any information relating to the production of antibodies as evidenced by the statement in the Office Action "Sala *et al.* does not teach generating antibodies with the HIV envelope protein" (see Office Action at page 9, lines 8-9). Applicants therefore submit that neither of the cited references discloses all of the limitations of either claims 24 or 25.

**Rejections under 35 U.S.C. 103(a)**

Claims 6 and 16 were rejected under 35 U.S.C. 103(a) as being unpatentable over Sala *et al.* and Haynes *et al.* (US 5,019,387). Claims 6 and 16 have been cancelled therefore the rejection is moot.

In light of substitute claim 35, Applicants note that the Office Action rejected claim 6 because Sala *et al.* disclose a buffer used to preserve DNA, clones and envelope proteins and purportedly this buffer would be a pharmaceutically acceptable carrier. Applicants bring to the Examiner's attention that the cited references do not even not even disclose the ingredients of the buffer used to store the nucleic acids, etc. It is therefore not possible to determine whether the contents would qualify as pharmaceutically acceptable carriers. Nonetheless, most buffers used to store nucleic acids and proteins contain toxic agents. For example, most buffers used for storing nucleic acid samples typically contain Tris (Sambrook *et al.* (2000), Molecular Cloning - A Laboratory Manural, Cold Spring Harbor Laboratory Press). Tris is a known hepatotoxin (Wiedersberg and Pawlowski (1979) Helv. Paediatr. *Act* 34: 53-62) and when administered in concentrations commonly used as a buffer in physiological salines, Tris can exert toxic effects on neuromuscular transmission in smooth and cardiac muscle (Gillespie and McKnight (1976) J. Physiol. 259, 561-573).

With regard to substitute claim 36, Applicants note that claim 16 was rejected as being unpatentable because the skilled artisan would have been motivated to combine the disclosure of Haynes *et al.* relating to induction of antibodies with HIV proteins, with the disclosure of the envelope sequences of Sala *et al.* to arrive at the claimed invention. Applicants bring to the attention of the Examiner that Sala *et al.* does not disclose an HIV envelope protein meeting the limitations of the pending claims and is not combinable with the remaining cited references.

**Conclusion**

The foregoing amendments and remarks are being made to place the application in condition for allowance. Applicants respectfully request reconsideration and the timely allowance of the pending claims. A favorable action is awaited. Should the Examiner find that an interview would be helpful to further prosecution of this application, they are invited to telephone the undersigned at their convenience.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "**Version With Markings to Show Changes Made**" as required.

**Except** for issue fees payable under 37 C.F.R. 1.18, the Commissioner is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. 1.16 and 1.17 which my be required, including any required extension of time fees, or

credit any overpayment to Deposit Account 50-0310. This paragraph is intended to be a **Constructive Petition for Extension of Time** in accordance with 37 C.F.R. 1.136(a)(3).

Respectfully submitted
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Dated: **December 18, 2002**
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## VERSION WITH MARKINGS TO SHOW CHANGES MADE

**In the Specification:**

**The paragraph beginning on page 4, line 14 has been replaced with the following paragraph:**

Figure 3 (A): Inhibition of Reference 2-mediated neutralization of pseudoviruses by synthetic V3 peptides. The neutralization endpoints for 90% neutralization were calculated as described previously (Quinnan *et al.*, 1999; Quinnan *et al.*, 1998; Zhang *et al.*, 1999; Park *et al.*, 1998). Results shown are means of triplicate determinations. Dose-response effects of R2 linear 17-mer (open square) and cyclic (closed square) **(SEQ ID NO: 2)** and the 93TH966.8 cyclic (shaded square) **(SEQ ID NO: 4)** V3 peptides on neutralization of clone R2 pseudovirus. The peptide concentrations are 3 x 10 raised to the indicated power.

**The paragraph beginning on page 7, line 6 has been replaced with the following paragraph:**

Polypeptides and peptides comprising any single domain may be of variable length but include the amino acid residues of Table 3 (SEQ ID NO: 1) which differ from previously sequenced envelope proteins. For instance, peptides of the invention which include all or part of the V3 domain may comprise the sequence: PM $X_1X_2X_3X_4X_5X_6X_7X_8X_9X_{10}$Q **(SEQ ID NO: 5)**, wherein $X_1$-$X_{10}$ are any natural or non-natural amino acids (P refers to Proline, M refers to methionine and Q refers to Glutamine). Non-natural amino acids include, for example, beta-alanine (beta-Ala), or other omega-amino acids, such as 3-amino propionic, 2,3-diamino propionic (2,3-diaP), 4-amino butyric and so forth, alpha-aminisobutyric acid (Aib), sarcosine (Sat), ornithine (Orn), citrulline (Cit), t-butylalanine (t-BuA), t-butylglycine (t-BuG), N-methylisoleucine (N-MeIle), phenylglycine (Phg) and cyclohexylalanine (Cha), norleucine (Nle), cysteic acid (Cya) 2-naphthylalanine (2-Nal); 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (Tic); beta-2-thienylalanine (Thi); and methionine sulfoxide (MSO). Preferably, peptides of the invention are 60%, 70%, 80% or more preferably, 90% identical to the V3 region of the HIV envelope protein of Table 3 (SEQ ID NO:1). Accordingly, V3 peptides of the invention comprise about 13 amino acids but may be 14, 15, 17, 20, 25, 30, 35, 36, 39, 40, 45, 50 or more amino acids in length. In one embodiment, a V3 peptide of 13 amino acids in length consists of the sequence PMGPGRAFYTTGQ (amino acids 313-325 of Table 3 (SEQ ID NO:1).

**The table on page 36 has been replaced with the following table:**

Comparison of V3 Region Amino Acid Sequences of Clone R2 with Phenetic Subgroup Consensus Sequences 1 Through 13 and Clade A Through E Consensus Sequences*

| Clone, Subgroup or Clade | V3 Region Amino Acid Sequence |
|---|---|
| | NNTR.KSIPMGPGRAFYTTGQIIGDIRQAHC |
| R2 | ----.---HI---------D---------- |
| PHENETIC 1 (SEQ ID NO: 6) | ----.---SI-------A--E---------- |
| PHENETIC 2 (SEQ ID NO: 7) | ----.---SI-------A--K---------- |
| PHENETIC 3 (SEQ ID NO: 8) | ----.---RI---Q---A--D---------- |
| PHENETIC 4 (SEQ ID NO: 9) | ----.---HI-------A--K---------- |
| PHENETIC 5 (SEQ ID NO: 10) | K--RRR-H.I---------K---------- |
| PHENETIC 6 (SEQ ID NO: 11) | ----.T--TI---QV--R--K---------- |
| PHENETIC 7 (SEQ ID NO: 12) | KKM-.T-ARI----V-HK--K---S-TK-Y- |
| PHENETIC 8 (SEQ ID NO: 13) | ----.Q-THI---Q-L---.D---K------ |
| PHENETIC 9 (SEQ ID NO: 14) | ----.QGTHI-----Y----.N---------- |
| PHENETIC 10 (SEQ ID NO: 15) | ----.QRTSI-Q-QAL---.E-R------A- |
| PHENETIC 11 (SEQ ID NO: 16) | D-IKIQRT-I-Q-Q-L---RITGYI.G---- |
| PHENETIC 12 (SEQ ID NO: 17) | Q-K-.QGT-I-L-Q-L---R.-K----K--- |
| PHENETIC 13 (SEQ ID NO: 18) | ----.--VHI---Q---A--D---------- |
| CLADE A (SEQ ID NO: 19) | ----.---HI---------E---------- |
| CLADE B (SEQ ID NO: 20) | ----.---RI---QT-YA--D---------- |
| CLADE C (SEQ ID NO: 21) | ----.QRTHI---Q-L---.R---------- |
| CLADE D (SEQ ID NO: 22) | ----.T--TI---QV--R--D------K-Y- |
| CLADE E (SEQ ID NO: 23) | |